

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix:**Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease**

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HALT-PKD Study Team Members

In addition to the authors, the following investigators participated in the HALT Progression of Polycystic Kidney Disease (HALT PKD) Trials:

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Figure S1: Systolic and diastolic blood pressure and urine aldosterone by blood pressure control group. Mean (95% CI) systolic and diastolic blood pressure over time shows separation by group (Panel A). Urine aldosterone excretion (Panel B) over time by group is presented. Symbols represent the mean with 95% CI bars. Solid (Standard blood pressure) and dashed (Low blood pressure) lines represent model-based trajectories. Slope estimates for urine aldosterone are based on linear mixed models with natural log transformations on the outcome and converted to annual percent change (as described in the statistical analysis section). Numbers in parentheses on the x-axes represent sample sizes in Standard and Low blood pressure groups, respectively. Follow up time ranged from 5 to 8 years.

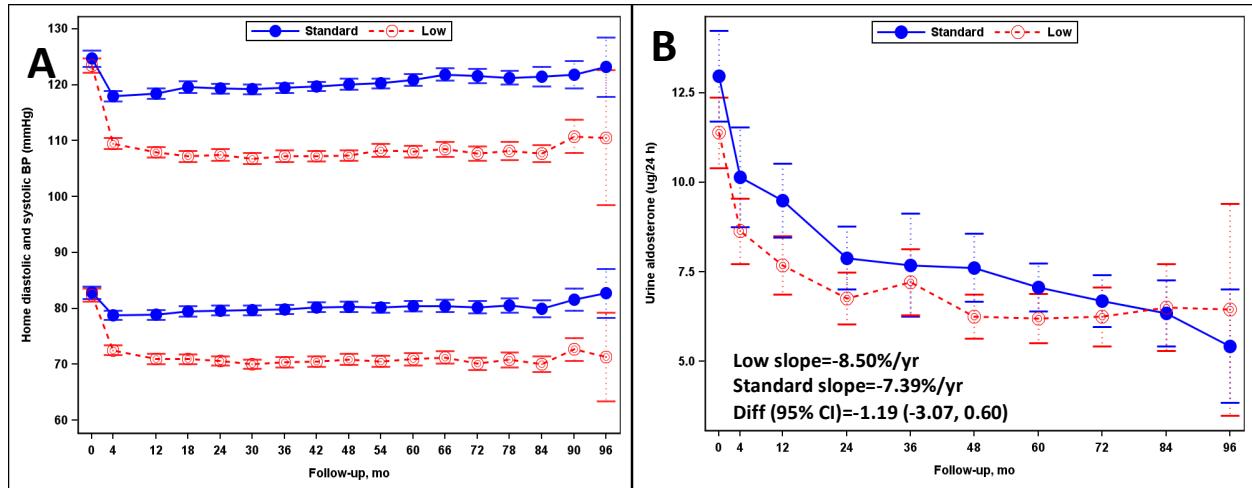


Figure S2: Urine albumin (Panel A), left ventricular mass index (Panel B), renal blood flow (Panel C), renal vascular resistance (1D), Physical Component Score (Panel E), Mental Component Score (Panel F) by blood pressure control group. Values represent means with 95% CI bars. Slope estimates for urine albumin are based on linear mixed models with natural log transformations on the outcome (as described in the statistical analysis section).

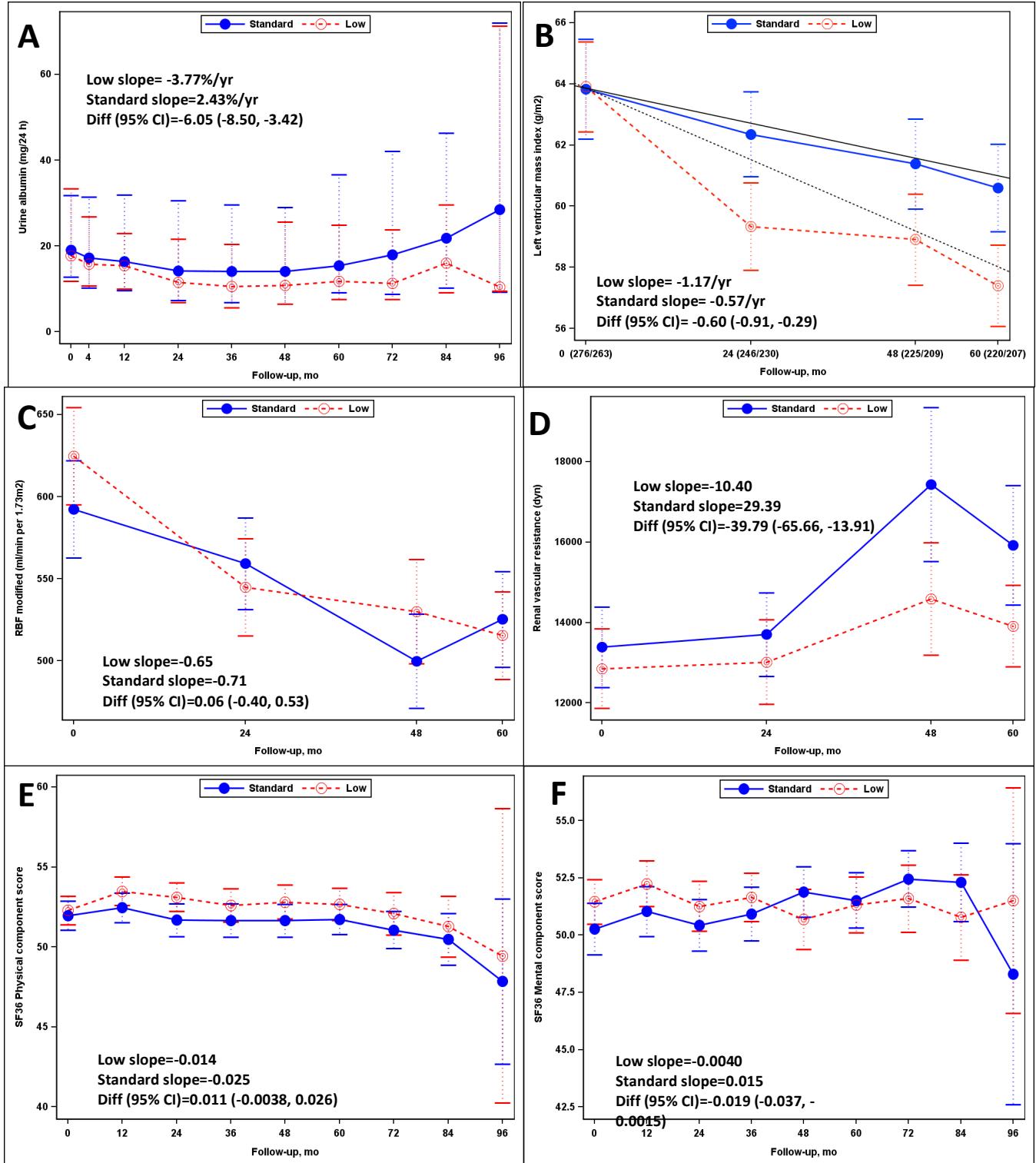


Figure S3: Systolic and diastolic blood pressure and urine aldosterone by treatment group.

Mean (95% CI) systolic and diastolic blood pressure over time shows no separation by group (Panel A). Urine aldosterone excretion (Panel B) over time by group is presented. Symbols represent the mean with 95% CI bars. Solid (Lisinopril/Telmisartan) and dashed (Lisinopril/Placebo) lines represent model-based trajectories. Slope estimates for urine aldosterone are based on linear mixed models with natural log transformations on the outcome and converted to annual percent change (as described in the statistical analysis section). Numbers in parentheses on the x-axes represent sample sizes in Lisinopril/Telmisartan and Lisinopril/Placebo groups, respectively. Follow up time ranged from 5 to 8 years.

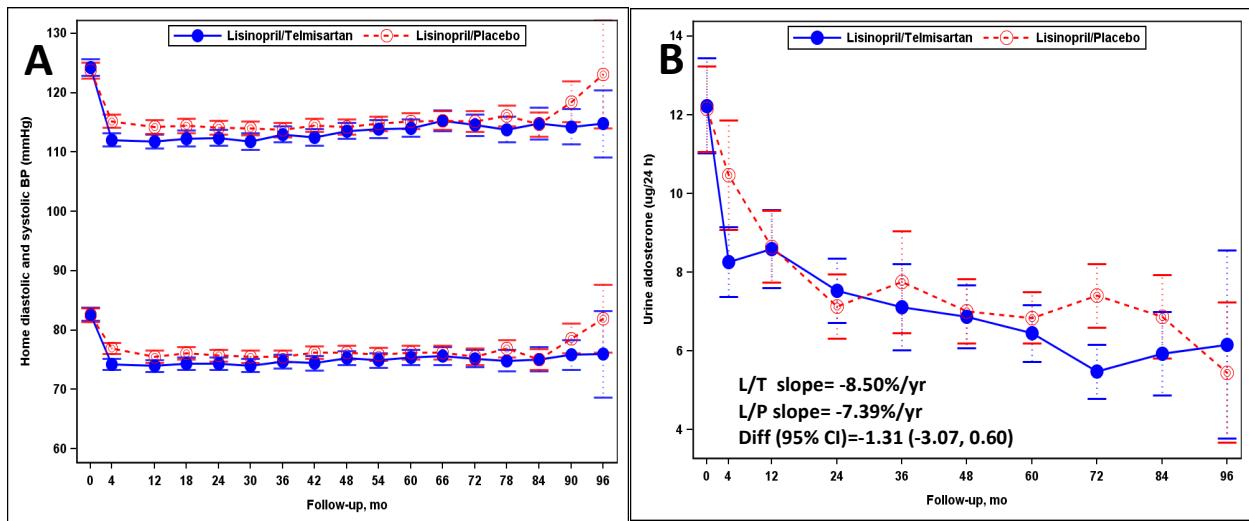


Figure S4: Urine albumin (Panel A), left ventricular mass index (Panel B), renal blood flow (Panel C), renal vascular resistance (Panel D), Physical Component Score (Panel E), Mental Component Score (Panel F) by treatment group. Values represent means with 95% CI bars. Slope estimates for urine albumin are based on linear mixed models with natural log transformations on the outcome (as described in the statistical analysis section).

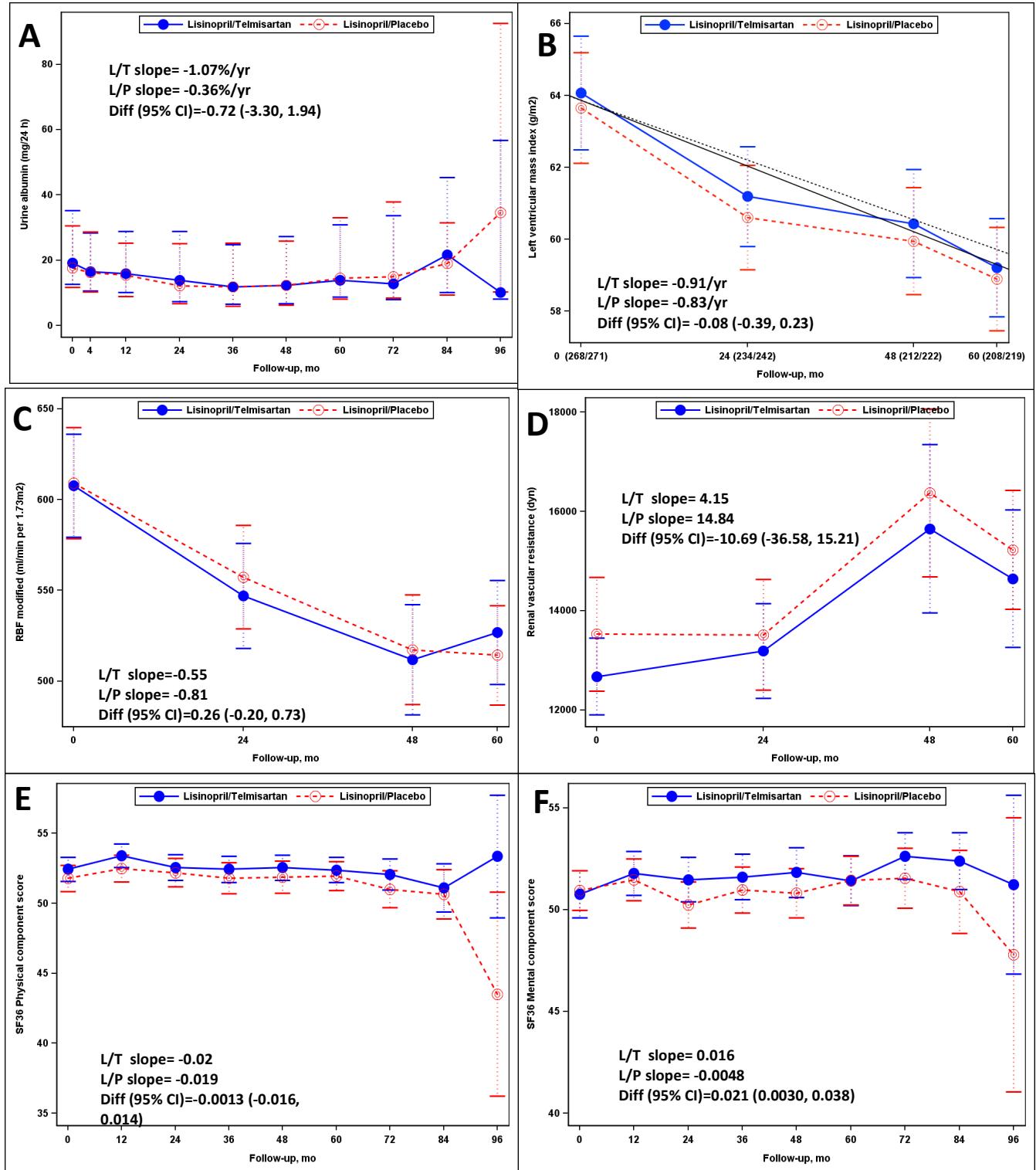


Table S1. Protocol for Addition of Antihypertensive Agents

| Step | Telmisartan | | Placebo | |
|----------------|---|------------------|---|---------------------|
| 1-4 | <u>ACE-I</u> | <u>ARB</u> | <u>ACE-I</u> | <u>Placebo</u> |
| | Lisinopril 5mg | Telmisartan 40mg | Lisinopril 5mg | <u>Placebo 40mg</u> |
| | Lisinopril 10mg | Telmisartan 40mg | Lisinopril 10mg | <u>Placebo 40mg</u> |
| | Lisinopril 20mg | Telmisartan 80mg | Lisinopril 20mg | <u>Placebo 80mg</u> |
| 5-6 | Lisinopril 40mg | | Telmisartan 80mg | |
| | Hydrochlorothiazide 12.5 mg - 25 mg QD | | Lisinopril 40mg | |
| | Metoprolol 50 mg BID | | <u>Placebo 80mg</u> | |
| | Metoprolol 100 mg BID | | Metoprolol 50 mg BID | |
| 7-9 | Metoprolol 200 mg BID | | Metoprolol 100 mg BID | |
| | Metoprolol 200 mg BID | | Metoprolol 200 mg BID | |
| | Non-dihydropyridine calcium channel blockers, clonidine, minoxidil, hydralazine at discretion of investigator | | Non-dihydropyridine calcium channel blockers, clonidine, minoxidil, hydralazine at discretion of investigator | |
| | | | | |
| 10 and onwards | | | | |

Table S2A. Additional categorical baseline demographic and clinical characteristics of study participants.

| | | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | | | Standard BP (n=284) | Low BP (n=274) | |
|-------------------------|----------------------------------|---------------------------------------|-----------------------------------|-----------|--|------------------------|-------------------|-----------|
| Measure | Category | n (%) | n (%) | p (chisq) | | n (%) | n (%) | p (chisq) |
| Race* | American Indian or Alaska Native | 1 (0.4%) | 5 (1.8%) | 0.1120 | | 4 (1.4%) | 2 (0.7%) | 0.4372 |
| | Asian | 2 (0.7%) | 4 (1.4%) | 0.4424 | | 3 (1.1%) | 3 (1.1%) | 0.9648 |
| | Black or African American | 6 (2.2%) | 8 (2.8%) | 0.6455 | | 7 (2.5%) | 7 (2.6%) | 0.9458 |
| | White or Caucasian | 255 (93.4%) | 262 (91.9%) | 0.5039 | | 258 (90.8%) | 259 (94.5%) | 0.0958 |
| | Some Other Race | 7 (2.6%) | 8 (2.8%) | 0.8592 | | 11 (3.9%) | 4 (1.5%) | 0.0781 |
| Highest education level | Some HS | 8 (3.0%) | 11 (3.9%) | 0.4340 | | 12 (4.2%) | 7 (2.6%) | 0.6115 |
| | Completed HS or Equivalent | 30 (11.1%) | 34 (11.9%) | | | 33 (11.6%) | 31 (11.4%) | |
| | Some college | 57 (21.0%) | 70 (24.6%) | | | 70 (24.6%) | 57 (21.0%) | |
| | Completed college | 103 (38.0%) | 112 (39.3%) | | | 104 (36.6%) | 111 (40.8%) | |
| | Graduate studies | 73 (26.9%) | 58 (20.4%) | | | 65 (22.9%) | 66 (24.3%) | |
| Marital status | Single | 78 (28.6%) | 84 (29.8%) | 0.2998 | | 82 (29.0%) | 80 (29.4%) | 0.2450 |
| | Married | 170 (62.3%) | 176 (62.4%) | | | 171 (60.4%) | 175 (64.3%) | |
| | Divorced | 23 (8.4%) | 15 (5.3%) | | | 24 (8.5%) | 14 (5.1%) | |
| | Separated | 2 (0.7%) | 3 (1.1%) | | | 3 (1.1%) | 2 (0.7%) | |
| | Widowed | 0 (0.0%) | 1 (0.4%) | | | 0 (0.0%) | 1 (0.4%) | |
| | Other | 0 (0.0%) | 3 (1.1%) | | | 3 (1.1%) | 0 (0.0%) | |
| Employment * | Student | 23 (8.4%) | 29 (10.2%) | 0.4770 | | 25 (8.8%) | 27 (9.9%) | 0.6694 |
| | Homemaker | 17 (6.2%) | 23 (8.1%) | 0.3989 | | 18 (6.3%) | 22 (8.0%) | 0.4388 |
| | Retired | 1 (0.4%) | 2 (0.7%) | 0.5880 | | 1 (0.4%) | 2 (0.7%) | 0.5418 |
| | Disabled | 1 (0.4%) | 6 (2.1%) | 0.0650 | | 4 (1.4%) | 3 (1.1%) | 0.7394 |
| | Full-Time Employment | 202 (74.0%) | 199 (69.8%) | 0.2737 | | 204 (71.8%) | 197 (71.9%) | 0.9860 |
| | Part-Time Employment | 31 (11.4%) | 35 (12.3%) | 0.7351 | | 34 (12.0%) | 32 (11.7%) | 0.9147 |
| | Other | 7 (2.6%) | 7 (2.5%) | 0.9350 | | 8 (2.8%) | 6 (2.2%) | 0.6358 |
| Diagnosis due to | Screening | 102 (37.5%) | 104 (36.5%) | 0.5863 | | 113 (39.8%) | 93 (34.1%) | 0.2171 |
| | Hypertension | 42 (15.4%) | 44 (15.4%) | | | 36 (12.7%) | 50 (18.3%) | |
| | Pain | 39 (14.3%) | 37 (13.0%) | | | 42 (14.8%) | 34 (12.5%) | |
| | Incidental imaging | 33 (12.1%) | 34 (11.9%) | | | 37 (13.0%) | 30 (11.0%) | |

| | | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | | | Standard BP (n=284) | Low BP (n=274) | |
|---------------------------------|------------------|---------------------------------------|-----------------------------------|-----------|--|------------------------|-------------------|-----------|
| Measure | Category | n (%) | n (%) | p (chisq) | | n (%) | n (%) | p (chisq) |
| | Other | 19 (7.0%) | 31 (10.9%) | | | 26 (9.2%) | 24 (8.8%) | |
| | Hematuria | 19 (7.0%) | 21 (7.4%) | | | 15 (5.3%) | 25 (9.2%) | |
| | Routine physical | 8 (2.9%) | 10 (3.5%) | | | 10 (3.5%) | 8 (2.9%) | |
| | UTI | 10 (3.7%) | 4 (1.4%) | | | 5 (1.8%) | 9 (3.3%) | |
| Diagnosis of ADPKD, Mode | Ultrasound | 199 (73.2%) | 202 (70.9%) | 0.1313 | | 205 (72.2%) | 196 (71.8%) | 0.9724 |
| | CT | 37 (13.6%) | 51 (17.9%) | | | 46 (16.2%) | 42 (15.4%) | |
| | MRI | 15 (5.5%) | 18 (6.3%) | | | 17 (6.0%) | 16 (5.9%) | |
| | IVP | 10 (3.7%) | 8 (2.8%) | | | 7 (2.5%) | 11 (4.0%) | |
| | Unknown | 4 (1.5%) | 6 (2.1%) | | | 5 (1.8%) | 5 (1.8%) | |
| | Other | 5 (1.8%) | 0 (0.0%) | | | 3 (1.1%) | 2 (0.7%) | |
| | X-Ray | 2 (0.7%) | 0 (0.0%) | | | 1 (0.4%) | 1 (0.4%) | |
| Family History of ADPKD | Yes | 237 (86.8%) | 242 (84.9%) | 0.5197 | | 244 (85.9%) | 235 (85.8%) | 0.9597 |
| At Screening | | | | | | | | |
| Antihypertensive medication use | | | | | | | | |
| Any ARB | Yes | 44 (17.2%) | 46 (17.6%) | 0.8958 | | 45 (17.2%) | 45 (17.6%) | 0.9196 |
| Any Ace Inhibitor | Yes | 128 (50.0%) | 124 (47.5%) | 0.5711 | | 135 (51.7%) | 117 (45.7%) | 0.1709 |
| Any Alpha Blocker | Yes | 8 (3.1%) | 15 (5.7%) | 0.1482 | | 10 (3.8%) | 13 (5.1%) | 0.4918 |
| Any Beta Blocker | Yes | 37 (14.5%) | 39 (14.9%) | 0.8752 | | 32 (12.3%) | 44 (17.2%) | 0.1137 |
| Any Calcium Blocker | Yes | 21 (8.2%) | 25 (9.6%) | 0.5829 | | 27 (10.3%) | 19 (7.4%) | 0.2432 |
| Any Diuretic | Yes | 23 (9.0%) | 28 (10.7%) | 0.5062 | | 27 (10.3%) | 24 (9.4%) | 0.7116 |

Table S2B. Additional numeric baseline demographic and clinical characteristics of study participants.

| | Lisinopril/Telmisartan (n=273) | | Lisinopril/Placebo (n=285) | | | Standard BP (n=284) | | Low BP (n=274) | | |
|---------------------------------------|-----------------------------------|---------------|-------------------------------|---------------|---------|------------------------|---------------|-------------------|---------------|---------|
| Measure | n | Mean ± SD | n | Mean ± SD | p (F) | n | Mean ± SD | n | Mean ± SD | p (F) |
| At Screening | | | | | | | | | | |
| Age at the time of PKD diagnosis | 271 | 27.8 ± 10.0 | 284 | 27.3 ± 10.0 | 0.5149 | 283 | 27.1 ± 9.7 | 272 | 28.0 ± 10.2 | 0.2803 |
| Age at the time of HTN diagnosis | 269 | 30.5 ± 8.9 | 285 | 30.5 ± 8.8 | 0.9868 | 282 | 30.2 ± 8.7 | 272 | 30.9 ± 9.1 | 0.3504 |
| Height (cm) | 270 | 173.8 ± 10.3 | 277 | 173.7 ± 10.1 | 0.9167 | 280 | 173.6 ± 10.5 | 267 | 174.0 ± 9.8 | 0.7126 |
| BSA (m ²) | 270 | 2.0 ± 0.2 | 276 | 2.0 ± 0.2 | 0.4781 | 279 | 2.0 ± 0.2 | 267 | 2.0 ± 0.2 | 0.9585 |
| Office Systolic BP (mmHg) | 271 | 122.4 ± 15.0 | 280 | 122.1 ± 13.7 | 0.7804 | 282 | 122.6 ± 14.9 | 269 | 121.8 ± 13.8 | 0.5292 |
| Office Diastolic BP (mmHg) | 271 | 78.2 ± 12.3 | 280 | 77.0 ± 11.1 | 0.1946 | 282 | 78.1 ± 11.7 | 269 | 77.1 ± 11.7 | 0.3362 |
| Office MAP | 271 | 93.0 ± 12.5 | 280 | 92.0 ± 11.1 | 0.3317 | 282 | 92.9 ± 12.0 | 269 | 92.0 ± 11.6 | 0.3726 |
| Hemoglobin g/dL | 270 | 14.2 ± 1.2 | 281 | 14.1 ± 1.3 | 0.4626 | 282 | 14.1 ± 1.3 | 269 | 14.1 ± 1.2 | 0.9105 |
| Urea Nitrogen (BUN) mg/dL | 273 | 15.4 ± 4.6 | 284 | 15.1 ± 4.6 | 0.4209 | 283 | 15.2 ± 4.9 | 274 | 15.3 ± 4.3 | 0.9160 |
| Total CO ₂ mEq/L or mmol/L | 273 | 27.1 ± 2.3 | 285 | 27.0 ± 2.3 | 0.6766 | 284 | 27.1 ± 2.3 | 274 | 27.1 ± 2.4 | 0.8402 |
| At Baseline | | | | | | | | | | |
| Home Systolic BP (mmHg) | 189 | 124.3 ± 9.8 | 184 | 123.8 ± 9.2 | 0.6238 | 181 | 124.7 ± 9.8 | 192 | 123.4 ± 9.1 | 0.1971 |
| Home Diastolic BP (mmHg) | 189 | 82.7 ± 7.6 | 184 | 82.5 ± 7.9 | 0.8249 | 181 | 82.8 ± 7.6 | 192 | 82.4 ± 7.9 | 0.5773 |
| Office Systolic BP (mmHg) | 271 | 127.0 ± 14.1 | 283 | 126.4 ± 13.6 | 0.6552 | 281 | 127.2 ± 14.0 | 273 | 126.2 ± 13.8 | 0.4024 |
| Office Diastolic BP (mmHg) | 271 | 80.7 ± 11.8 | 283 | 79.6 ± 10.3 | 0.2780 | 281 | 80.8 ± 11.2 | 273 | 79.4 ± 10.9 | 0.1439 |
| Height-adjusted TKV | 267 | 724.5 ± 431.7 | 273 | 660.8 ± 369.4 | 0.2256† | 276 | 705.3 ± 406.0 | 264 | 678.7 ± 398.7 | 0.4437† |
| Urine sodium/potassium ratio | 261 | 3.4 ± 1.6 | 275 | 3.4 ± 1.6 | 0.9324 | 273 | 3.4 ± 1.6 | 263 | 3.4 ± 1.6 | 0.7056 |
| Serum Creatinine | 273 | 1.0 ± 0.2 | 284 | 0.9 ± 0.2 | 0.2681 | 283 | 1.0 ± 0.2 | 274 | 1.0 ± 0.2 | 0.9343 |
| S. sodium mEq/L | 273 | 139.2 ± 2.1 | 285 | 139.1 ± 2.2 | 0.5921 | 284 | 139.1 ± 2.3 | 274 | 139.3 ± 2.0 | 0.3154 |

| | Lisinopril/Telmisartan (n=273) | | Lisinopril/Placebo (n=285) | | | Standard BP (n=284) | | Low BP (n=274) | | |
|----------------------------|-----------------------------------|------------------|-------------------------------|------------------|--------|------------------------|------------------|-------------------|------------------|--------|
| Measure | n | Mean ± SD | n | Mean ± SD | p (F) | n | Mean ± SD | n | Mean ± SD | p (F) |
| Urine sodium mEq/24 hrs | 265 | 177.2 ± 75.8 | 277 | 178.9 ± 83.7 | 0.8012 | 276 | 177.9 ± 80.7 | 266 | 178.2 ± 79.2 | 0.9666 |
| Urine potassium mEq/24 hrs | 261 | 58.2 ± 25.7 | 275 | 58.5 ± 28.2 | 0.8832 | 273 | 58.4 ± 26.1 | 263 | 58.2 ± 27.8 | 0.9291 |
| Renal vascular resistance | 181 | 12675.9 ± 5308.9 | 198 | 13527.4 ± 8202.0 | 0.2357 | 190 | 13386.8 ± 7023.6 | 189 | 12853.3 ± 6935.8 | 0.4573 |
| Serum creatinine at F5 | 253 | 1.0 ± 0.2 | 263 | 1.0 ± 0.2 | 0.1408 | 263 | 1.0 ± 0.2 | 253 | 1.0 ± 0.2 | 0.2035 |
| CKD EPI eGFR at F5 | 253 | 87.5 ± 19.0 | 263 | 90.2 ± 18.0 | 0.0950 | 263 | 90.7 ± 18.7 | 253 | 87.0 ± 18.2 | 0.0260 |

†p-value on the comparison of the transformed variable

Table S3. Open label anti-hypertensive agents added at any time after maximal doses of lisinopril and telmisartan/placebo

| | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | | Standard BP (n=284) | Low BP (n=273) |
|-------------------------------------|---------------------------------------|--------------------------------|---------|------------------------|-------------------|
| | n (%) | n (%) | p value | n (%) | n (%) |
| Diuretic | 81 (29.7%) | 118 (41.4%) | 0.0038 | 76 (26.8%) | 123 (44.9%) |
| Beta- or alpha/beta blocker | 59 (21.6%) | 68 (23.9%) | 0.5267 | 41 (14.4%) | 86 (31.4%) |
| Calcium channel blocker | 17 (6.2%) | 26 (9.1%) | 0.1998 | 15 (5.3%) | 28 (10.2%) |
| Central alpha 2 adrenergic agonist | 8 (2.9%) | 5 (1.8%) | 0.3573 | 4 (1.4%) | 9 (3.3%) |
| Vasodilator | 6 (2.2%) | 9 (3.2%) | 0.4833 | 5 (1.8%) | 10 (3.6%) |
| Alpha 1 adrenergic receptor blocker | 1 (0.4%) | 1 (0.4%) | 0.9757 | 0 (0.0%) | 2 (0.7%) |

Table S4. Lisinopril and Telmisartan dose by blood pressure control groups.

| Measure | Timepoint | Standard BP | | Low BP | |
|-----------------------------------|-----------------------------------|--------------------|------------------|---------------|------------------|
| | | n | Mean ± SD | n | Mean ± SD |
| Lisinopril dose (mg/day) | B1 | 250 | 6.2 ± 3.6 | 256 | 5.9 ± 2.5 |
| | F12 | 169 | 15.6 ± 14.8 | 228 | 25.0 ± 14.5 |
| | F24 | 179 | 15.1 ± 14.2 | 217 | 25.7 ± 14.2 |
| | F36 | 176 | 15.3 ± 14.6 | 203 | 25.6 ± 14.6 |
| | F48 | 172 | 14.9 ± 15.0 | 199 | 25.4 ± 14.7 |
| | F60 | 166 | 14.3 ± 14.0 | 175 | 24.9 ± 14.9 |
| | F72 | 118 | 16.1 ± 15.7 | 115 | 23.8 ± 15.1 |
| | F84 | 66 | 15.1 ± 16.2 | 65 | 23.3 ± 15.7 |
| | F96 | 12 | 6.0 ± 11.2 | 6 | 20.0 ± 21.9 |
| | Telmisartan/Placebo dose (mg/day) | 252 | 40.2 ± 4.0 | 256 | 39.9 ± 1.3 |
| Telmisartan/Placebo dose (mg/day) | F12 | 216 | 50.9 ± 19.1 | 230 | 66.6 ± 20.0 |
| | F24 | 214 | 50.9 ± 19.3 | 224 | 65.7 ± 19.2 |
| | F36 | 206 | 51.4 ± 19.9 | 214 | 66.4 ± 21.2 |
| | F48 | 193 | 51.4 ± 20.6 | 206 | 65.8 ± 19.2 |
| | F60 | 184 | 48.4 ± 22.8 | 183 | 59.5 ± 23.7 |
| | F72 | 124 | 46.9 ± 25.5 | 125 | 59.3 ± 24.9 |
| | F84 | 69 | 38.8 ± 24.5 | 70 | 52.3 ± 25.3 |
| | F96 | 10 | 20.0 ± 21.1 | 9 | 31.1 ± 17.6 |

Table S5. Symptoms by treatment arm and blood pressure control groups. Participants were asked about the occurrence of symptoms every 3 months per protocol.

| | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | Standard BP (n=284) | Low BP (n=274) |
|---|---------------------------------------|-----------------------------------|------------------------|-------------------|
| Follow-up duration (average years) | 5.6 | 5.7 | 5.7 | 5.6 |
| Symptoms | | | | |
| Malaise/feeling ill | | | | |
| Number of events | 1106 | 1212 | 1158 | 1160 |
| Number of participants affected | 229 (83.9%) | 233 (81.8%) | 230 (81.0%) | 232 (84.7%) |
| Headache | | | | |
| Number of events | 1420 | 1789 | 1701 | 1508 |
| Number of participants affected | 217 (79.5%) | 233 (81.8%) | 228 (80.3%) | 222 (81.0%) |
| Nasal congestion | | | | |
| Number of events | 1500 | 1655 | 1597 | 1558 |
| Number of participants affected | 231 (84.6%) | 241 (84.6%) | 233 (82.0%) | 239 (87.2%) |
| Dizziness/lightheadedness | | | | |
| Number of events | 1105 | 1149 | 911 | 1343 |
| Number of participants affected | 210 (76.9%) | 208 (73.0%) | 197 (69.4%)§ | 221 (80.7%) |
| Cough | | | | |
| Number of events | 975 | 1159 | 990 | 1144 |
| Number of participants affected | 214 (78.4%) | 229 (80.4%) | 223 (78.5%) | 220 (80.3%) |
| Joint pain/aches | | | | |
| Number of events | 1167 | 1270 | 1399 | 1038 |
| Number of participants affected | 198 (72.5%) | 197 (69.1%) | 204 (71.8%) | 191 (69.7%) |
| Kidney pain (back or flank) | | | | |
| Number of events | 1774 | 2250 | 2117 | 1907 |
| Number of participants affected | 214 (78.4%) | 221 (77.5%) | 227 (79.9%) | 208 (75.9%) |

Table S6. Complete List of Serious Adverse Events in Study A by Randomization Group[#]

| | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | Standard Blood Pressure (n=284) | Low Blood Pressure (n=274) |
|--|---------------------------------------|-----------------------------------|--|----------------------------------|
| Follow-up duration (average years) | 5.6 | 5.7 | 5.7 | 5.6 |
| Acute kidney injury events, participants (%) | 15, 13 (4.8%) | 19, 16 (5.6%) | 17, 13 (4.6%) | 17, 16 (5.8%) |
| Hyperkalemia – Any events, participants (%) | 13, 11 (4.0%) | 6, 5 (1.8%) | 11, 9 (3.2%) | 8, 7 (2.6%) |
| Hyperkalemia – Mild events, participants (%) | 7, 7 (2.6%) | 5, 4 (1.4%) | 8, 7 (2.5%) | 4, 4 (1.5%) |
| Hyperkalemia – Moderate events, participants (%) | 5, 4 (1.5%) | 1, 1 (0.4%) | 3, 3 (1.1%) | 3, 2 (0.7%) |
| Hyperkalemia – Serious events, participants (%) | 1, 1 (0.4%) | 0, 0 (0.0%) | 0, 0 (0.0%) | 1, 1 (0.4%) |
| Hospitalizations number, incidence per 100 py | 85, 5.55 | 128, 7.92 | 120, 7.43 | 93, 6.07 |
| Cardiac-related hospitalizations number, incidence per 100 py | 13, 0.85 | 9, 0.56 | 13, 0.80 | 9, 0.59 |
| Cancer events, participants (%) | 4, 4 (1.5%) | 4, 4 (1.4%) | 2, 2 (0.7%) | 6, 6 (2.2%) |
| Serious Adverse Events | | | | |
| Death[^], total events, participants (%) | 1 (0.4) | 1 (0.4) | 2 (0.7%) | 0 (0.0%) |
| Cardiac disorders, total events, participants (%) | 9, 6 (2.2%) | 6, 5 (1.8%) | 12, 8 (2.8%) | 3, 3 (1.1%) |
| Coronary artery disease, events, participants (%) | 2, 2 (0.7%) | 1, 1 (0.4%) | 2, 2 (0.7%) | 1, 1 (0.4%) |
| Arrhythmias, events, participants (%) | 4, 2 (0.7%) | 4, 3 (1.1%) | 7, 4 (1.4%) | 1, 1 (0.4%) |
| Other, events, participants (%) | 3, 3 (1.1%) | 1, 1 (0.4%) | 3, 3 (1.1%) | 1, 1 (0.4%) |
| Gastrointestinal disorders, total events, participants (%) | 11, 8 (2.9%) | 17, 12 (4.2%) | 21, 16 (5.6%) [*] | 7, 4 (1.5%) |
| Abdominal pain, events, participants (%) | 3, 3 (1.1%) | 9, 6 (2.1%) | 7, 6 (2.1%) | 5, 3 (1.1%) |
| Nervous system disorders | | | | |
| Cerebrovascular, events, participants (%) | 3, 2 (0.7%) | 2, 2 (0.7%) | 2, 2 (0.7%) | 3, 2 (0.7%) |
| Headache, events, participants (%) | 1, 1 (0.4%) | 5, 4 (1.4%) | 4, 3 (1.1%) | 2, 2 (0.7%) |
| Syncope/dizziness, events, participants (%) | 1, 1 (0.4%) | 1, 1 (0.4%) | 1, 1 (0.4%) | 1, 1 (0.4%) |
| Other, events, participants (%) | 5, 4 (1.5%) | 4, 4 (1.4%) | 7, 6 (2.1%) | 2, 2 (0.7%) |

| | Lisinopril/ Telmisartan (n=273) | Lisinopril/ Placebo (n=285) | Standard Blood Pressure (n=284) | Low Blood Pressure (n=274) |
|---|---------------------------------------|-----------------------------------|--|----------------------------------|
| Renal and Urinary system disorders | 14, 12 (4.4%) | 15, 14 (4.9%) | 16, 14 (4.9%) | 13, 12 (4.4%) |
| Renal hemorrhage/hematuria, events, participants (%) | 1, 1 (0.4%) | 1, 1 (0.4%) | 1, 1 (0.4%) | 1, 1 (0.4%) |
| Nephrolithiasis/renal colic, events, participants (%) | 3, 3 (1.1%) | 4, 4 (1.4%) | 7, 7 (2.5%)* | 0, 0 (0.0%) |
| Urinary tract obstruction, events, participants (%) | 2, 2 (0.7%) | 0, 0 (0.0%) | 1, 1 (0.4%) | 1, 1 (0.4%) |
| Acute Kidney injury, events, participants (%) | 0, 0 (0.0%) | 1, 1 (0.4%) | 1, 1 (0.4%) | 0, 0 (0.0%) |
| Other, events, participants (%) | 8, 7 (2.6%) | 9, 8 (2.8%) | 6, 5 (1.8%) | 11, 10 (3.6%) |

* Percentage of participants affected significantly different from low BPblood pressure group ($p < 0.05$).

#All Serious Adverse Events were classified using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

^Causes of death were: cardiac arrest and neurological

Table S7. Lisinopril and Telmisartan dose by treatment groups.

| Measure | Timepoint | Lisinopril/ Telmisartan | | Lisinopril/ Placebo | |
|-----------------------------------|------------------|------------------------------------|------------------|--------------------------------|------------------|
| | | n | Mean ± SD | n | Mean ± SD |
| Lisinopril dose (mg/day) | B1 | 251 | 6.0 ± 3.2 | 255 | 6.0 ± 3.0 |
| | F12 | 177 | 18.0 ± 15.3 | 220 | 23.4 ± 15.0 |
| | F24 | 174 | 17.7 ± 14.8 | 222 | 23.5 ± 14.9 |
| | F36 | 162 | 17.0 ± 14.9 | 217 | 23.7 ± 15.3 |
| | F48 | 168 | 16.8 ± 16.0 | 203 | 23.7 ± 14.8 |
| | F60 | 153 | 16.4 ± 15.2 | 188 | 22.5 ± 15.1 |
| | F72 | 102 | 15.6 ± 14.7 | 131 | 23.3 ± 16.0 |
| | F84 | 56 | 18.0 ± 16.2 | 75 | 20.0 ± 16.7 |
| | F96 | 8 | 7.2 ± 13.7 | 10 | 13.5 ± 18.4 |
| Telmisartan/Placebo dose (mg/day) | B1 | 251 | 39.8 ± 2.2 | 257 | 40.3 ± 3.5 |
| | F12 | 215 | 55.3 ± 20.6 | 231 | 62.5 ± 20.9 |
| | F24 | 212 | 54.3 ± 20.5 | 226 | 62.4 ± 20.0 |
| | F36 | 199 | 53.8 ± 22.7 | 221 | 63.8 ± 20.0 |
| | F48 | 191 | 53.6 ± 21.1 | 208 | 63.7 ± 20.1 |
| | F60 | 174 | 50.0 ± 23.5 | 193 | 57.4 ± 23.7 |
| | F72 | 114 | 48.4 ± 26.6 | 135 | 57.2 ± 24.7 |
| | F84 | 65 | 42.5 ± 26.1 | 74 | 48.4 ± 25.2 |
| | F96 | 7 | 22.9 ± 21.4 | 12 | 26.7 ± 19.7 |